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The Role of IL-17 in Vitiligo: A Review

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Abstract

IL-17 is involved in the pathogenesis of several autoimmune diseases, however its role in vitiligo has not been well defined. Emerging human and mouse studies have demonstrated that systemic, tissue, and cellular levels of IL-17 are elevated in vitiligo. Many studies have also shown significant positive correlations between these levels and disease activity, extent, and severity. Treatments that improve vitiligo, such as ultraviolet B phototherapy, also modulate IL-17 levels. This review synthesizes our current understanding of how IL-17 may influence the pathogenesis of autoimmune vitiligo at the molecular level. This has implications for defining new vitiligo biomarkers and treatments.

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Conflicts of Interest

Dr. Liao receives funding from the NIH (R01AR065174, U01AI119125) and serves as a research investigator for Abbvie, Janssen, and Novartis.

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Keywords

Interleukin-17; IL-17; Vitiligo

1. Introduction

The cytokine interleukin-17 has been increasingly implicated in the pathogenesis of several immune-mediated diseases. Whether interleukin-17 plays a role in the etiology of vitiligo, an autoimmune pigmentary skin disorder, has not been well defined in the literature. In this review, we synthesize molecular data from vitiligo patients and animal models of vitiligo to demonstrate that interleukin-17 may play an important role in vitiligo pathogenesis. This has implications not only for our understanding of the biology of vitiligo, but also for defining new biomarkers and treatments.

2. Interleukin-17

Interleukin-17 is a family of six cytokines that includes IL-17A through IL-17F[1]. IL-17A (also known as IL-17) and IL-17F are the most homologous to one another, as well as the best studied for their roles in immune modulation[2]. The two cytokines are expressed by the Th17 subset of CD4+ helper T cells[3] and signal through IL-17RA and IL-17RC, heterodimeric receptors chiefly expressed on tissue fibroblasts and epithelial cells[4]. Despite strong sequence homology and similarly controlled expression patterns, IL-17A and IL-17F regulate distinct responses in vivo. For instance, studies in mice selectively deficient for either IL-17A or IL-17F have demonstrated that only IL-17A is required for the induction of experimental autoimmune encephalomyelitis (EAE). On the other hand, IL-17F and not IL-17A deficiency leads to an aberrant airway neutrophil response to allergen stimulus[5].

2.1. IL-17 in inflammatory disorders

Several inflammatory disorders have been attributed in part to pathogenic effects of the interleukin-17 family. Psoriasis is a chronic inflammatory skin condition marked by rapid epithelial cell turnover, dermal angiogenesis, and multi-immune cell infiltration. Elevated levels of IL-17A and IL-17F, along with other pro-inflammatory Th17 type cytokines, have been found in the sera and skin of psoriatic patients[6]. Phase III data evaluating the efficacy of secukinumab, an anti-IL-17A drug FDA-approved for psoriasis, have revealed that the drug has high efficacy with PASI75 (the proportion of patients in a trial achieving at least 75% reduction in psoriasis severity) ranging from 67% to 91% based on the dose given[7–10]. Phase I and II studies of anti-IL17A therapy in psoriasis have also documented dose-dependent reductions in keratinocyte proliferation, epidermal hyperplasia, and immune cell infiltration with simultaneous improvements in cellular and molecular disease biomarkers[11–14]. Additional clinical trials of biologic therapies antagonizing IL-17 or IL-17 receptor have also shown high efficacy in psoriasis[15–17].

Rheumatoid arthritis (RA) is characterized by chronic inflammation of joint synovial fluid that damages adjacent cartilage and bone over time. Elevated levels of IL-17 are observed in the sera and synovial fluid of patients, particularly in areas with larger T-cell

populations[18]. Furthermore, these levels correlate with disease severity and duration[19]. Human clinical trials of IL-17 blockade in RA have demonstrated a favorable response profile to the therapy, with reduced inflammatory marker levels, improved quality of life scores, and significant response rates[20]. Additional support for the cytokine's role in disease promotion comes from mouse models constructed with an IL-17 knockout. These mice develop considerably less arthritis[21,22]. Moreover, introduction of anti-IL-17 neutralizing antibodies directly reduces synovial inflammation and bone and cartilage erosion in mice with arthritis[23,24].

IL-17 has also recently been implicated in the pathogenesis of multiple sclerosis (MS), a non-rheumatic condition in which neurons of the central nervous system undergo autoimmune demyelination. MS subjects exhibit higher blood and CSF levels of IL-17 as compared to controls[25]. An intersection of the Th1 and Th17 pathways has been observed in mouse models of MS, wherein the transcription factors that govern both lineages are co-expressed in autoreactive CD4+ T cells that cross the blood brain barrier (BBB) and induce pathologic demyelination[26]. IL-17, in particular, disrupts junctions of the BBB via increased production of reactive oxygen species (ROS)[27].

Primary Sjogren's syndrome (pSS) is an autoimmune disorder marked by widespread chronic inflammation of exocrine glands that impairs tissue integrity and glandular secretion. Studies have reported a direct correlation between periductal infiltrating IL-17+ mononuclear cells and extent of exocrine gland involvement. In addition, higher IL-17 mRNA expression has been associated with greater severity minor salivary gland lesions. Lastly, lacrimal IL-17 is increased in patients with pSS relative to those with dry eye syndrome of other etiologies. Although yet unemployed, it has been suggested that targeting the IL-17/Th17 axis represents a credible therapeutic approach to pSS[28].

The role of IL-17 in inflammatory bowel disease remains controversial. Although once only thought of as proinflammatory, IL-17 has recently also been recognized to play a protective role in the intestine. A few studies using experimental IL-17A knock-out mice have demonstrated that these animals may undergo worsening of dextran sulfate sodium-induced colitis[29,30]. More importantly, clinical studies of antibodies targeting IL-17A and IL-17 receptor in Crohn's disease unexpectedly showed these agents to be either ineffective or disease worsening[31,32]. To explain this, it has been proposed that IL-17 inhibition in the intestines may paradoxically lead to an enhanced Th1 response marked by increased IFN-γ production[33]. On the other hand, functional studies of the small-molecule inhibitors Vidofludimus and Tofacitinib in IBD patients, which antagonize IL-17 among their other functions, have demonstrated efficacy. It is possible that the less selective IL-17 inhibition achieved by these small-molecule inhibitors is a more effective therapeutic strategy for IBD, although the reasons why are still unclear[34].

3. Vitiligo

Vitiligo is a disease of the pigment-producing cells, or melanocytes, that can result in varying patterns and degrees of skin depigmentation. The effect of genetics is thought to be complex and multifactorial, with several vitiligo susceptibility loci identified by genome-

wide association studies [35–38]. A study examining monozygotic twins reported a vitiligo concordance rate of 23%, suggesting a strong environmental contribution to the pathogenesis; however the etiology of vitiligo remains poorly understood[39]. Several groups have explored a neural hypothesis, uncovering so-called neurogenic inflammatory mediators such as NGF and NPY that may be directly toxic to melanocytes[40,41]. Antibody-mediated, cell-mediated, and cytokine-mediated mechanisms have all accumulated supportive evidence for an autoimmune hypothesis. Autoantibodies against tyrosine hydroxylase and various pigment cell-surface antigens that are specific to melanocytes have been identified in the sera of vitiligo patients [42,43]. Additionally, studies have supported a melanocyte-specific immune reaction driven by cytotoxic CD8+ T cells[44,45]. Lastly, Th1, Th2, and more recently Th17 type cytokines have been significantly quantified in the sera and skin of patients with vitiligo[46,47]. A final hypothesis suggests that hyperproduction of ROS may occur in affected melanocytes, directly damaging critical cellular components[48]. It appears that vitiligo pathogenesis involves a complex interplay between multiple systems, including genetic, neural, autoimmune, and redox pathways.

4. IL-17 Dynamics in Vitiligo

4.1. Human Studies

Several human studies have investigated the roles that Th17 cells and IL-17, the signature Th17 cytokine, play in vitiligo (Table 1):

4.1.1. Peripheral blood Th17 cells in vitiligo—Th17 cells are a subset of CD4+ T cells that secrete several immune modulatory substances, including IL-17, IL-21, IL-22, GM-CSF, and CCL20. These cells and their effector molecules have been implicated in the pathogenesis of various autoimmune diseases[49]. Two studies have investigated whether circulating Th17 cells are elevated in vitiligo patients. A cross-sectional study of 45 patients with active non-segmental vitiligo (NSV) compared to 45 age-, gender-, and race-matched healthy controls used flow cytometry to quantify peripheral blood Th17 cells. The abundance of these IL-17 producing cells was increased in vitiligo relative to control subjects ($p=0.001$) and positively correlated with affected body surface area ($r=0.0615$, $p<0.001$)[50]. A second cross-sectional study of 5 vitiligo patients did not report similar findings; however, their sample size was not sufficiently powered[51].

4.1.2. Serum levels of IL-17 in vitiligo—Seven studies quantified serum IL-17, with six showing strong evidence of higher levels in vitiligo and one not demonstrating any difference between vitiligo and control subjects. Zhou et al. detected significantly higher serum IL-17 in 45 subjects with active NSV versus 45 controls using ELISA ($p = 0.0145$) [50]. Two other studies reported similar findings, with 7-fold higher levels on average in vitiligo subjects[52,53]. One of these additionally uncovered significant positive correlations between serum IL-17 and both disease duration ($r=0.42$, $p=0.02$) and extent of body area involvement of vitiligo ($r=0.65$, $p<0.001$)[52].

Serum IL-17 levels have also been shown to be negatively correlated with age of disease onset ($r = -0.397$, $p = 0.011$) and positively correlated with extent of body area involvement ($r = 0.329$, $p= 0.038$) in 40 patients with vitiligo[54].

Systemic IL-17A was quantified by both ELISA and quantitative real-time PCR (qRT-PCR) in a case-control study of 84 NSV patients and 80 healthy controls. Vitiligo subjects were noted to have nearly 2-fold higher serum IL-17 compared to controls ($p<0.001$) that positively correlated with both Vitiligo Area Scoring Index (VASI) and Vitiligo Disease Activity (VDA)[55].

Another case-control study similarly quantified peripheral IL-17 levels of 80 vitiligo patients and 70 healthy controls, but also further subdivided the vitiligo group based on disease stage (60 active versus 20 stable). Serum IL-17 was noted to be 1.4-fold higher on average in the pooled vitiligo versus control groups and 1.2-fold higher in active versus stable stage vitiligo subjects ($p=0.001$ for both)[56]. In contrast, two other groups did not note any correlation between serum IL-17 and disease stage, although they had smaller sample sizes of only 15 vitiligo patients each[57,58]. Nevertheless, Habeb and colleagues did still report significantly higher serum IL-17 in vitiligo subjects compared to age- and sex-matched controls, as detected by RT-PCR ($p<0.01$). They also noted a significant difference in systemic IL-17 between subjects with positive versus negative family history of vitiligo and patients with early versus late onset of vitiligo[58].

4.1.3. IL-17+ mononuclear cells in vitiligo lesions—In addition to studies examining inflammatory markers within peripheral blood, a number of studies have focused on whether such markers are also elevated within affected skin tissue. Histologic examination of vitiliginous skin has revealed that the perilesional margins contain an infiltrate of activated cytotoxic T cells[59]. Provision of melanocyte antigen-specific stimulation to T cells isolated from perilesional skin biopsies of vitiligo has been noted to induce substantial numbers of IL-17-producing $CD8^+$ T cells in response from one patient[60]. Additional immunohistochemical and immunofluorescent studies have examined leading edge biopsies of vitiligo lesions and demonstrated greater numbers of IL-17A+ and IL-17A receptor+ staining in lesional compared to non-lesional vitiliginous skin[61,62].

4.1.4. Tissue expression of IL-17 mRNA in vitiligo lesions—Six studies have investigated whether tissue IL-17 mRNA expression is higher in vitiligo lesions compared to non-lesions. Lesional expression of IL-17 mRNA in NSV has been reported to be up to 7-fold higher, with perilesional expression 3-fold higher compared to non-lesional control skin[52,55,63]. The extent of body surface affected by vitiligo ($r=0.48$, $p<0.05$), disease duration ($r=0.45$, $p<0.015$), and serum IL-17 ($r=0.54$, $p=0.002$) have also been noted to positively correlate with tissue IL-17 expression[52]. Additionally, two studies demonstrated consistently higher IL-17 mRNA expression in leading edge biopsies of vitiliginous lesions compared to non-lesions via qRT-PCR[60,61].

Lastly, a trend toward increased IL-17 gene expression in the neutrophils of 15 vitiligo patients has also been reported[57].

4.1.5. NB-UVB therapy and IL-17, Th17 in vitiligo—Narrow-band ultraviolet B (NB-UVB) light therapy is considered a cornerstone of vitiligo treatment[64,65]. To explore a functional role for IL-17 and Th17 cells in vitiligo, a few studies have measured the effect of NB-UVB treatment on the two. One study found that after 12 weeks of NB-UVB treatment, IL-17 expression decreased by 33% lesionally and 50% perilesionally ($p<0.05$ for both). This was accompanied by significant reductions in VASI ($p<0.001$). Moreover, VASI was significantly positively correlated with systemic IL-17 levels at baseline and post-treatment[63].

Another group noted that serum IL-17 remained higher in vitiligo patients post NB-UVB relative to healthy controls, but that treated patients had a 7.5% reduction compared to their untreated counterparts ($p<0.001$) Their results suggest that NB-UVB treatment abrogates IL-17A secretion, which may in turn be responsible for the clinical improvement of vitiligo seen with NB-UVB therapy[56].

CO2 laser therapy has also been noted to lead to a significant reduction in circulating Th17 lymphocytes, serum IL-17, and IL-17 mRNA expression within cutaneous lesions[66].

4.1.6. Direct effects of exogenous IL-17 on melanocytes—To expand upon the correlative studies reporting elevated IL-17 in the sera and skin of vitiligo patients, one group investigated the direct functional effects of exogenous IL-17 on melanocytes. Kotobuki et al. showed that expression of MITF, an essential transcriptional regulator of melanogenesis, and its downstream genes was reduced by more than 10% in melanocytes treated with IL-17 ($p<0.01$). This trend was also seen for expression of the anti-apoptotic BCL2 molecule, with more than 20% reduction post IL-17-treatment ($p<0.05$). The authors also noted an approximately 30% decrease in melanin production from IL-17-treated melanocytes ($p<0.05$). Furthermore, IL-17 was observed to cause morphological shrinking of melanocytes, further contributing to decreased pigment production. Finally, IL-17 robustly induced expression of the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α in skin-resident keratinocytes and fibroblasts in a dose-dependent fashion ($p<0.05$). The authors suggested that IL-17 contributes to local depigmentation in autoimmune vitiligo via its antagonism of factors related to melanocyte function, reduction in melanogenesis, and dramatic induction of other Th17 type cytokines from dermal fibroblasts and keratinocytes[62].

4.2. Mouse Studies

Mouse models of vitiligo have also investigated the impact of IL-17 on disease development (Table 2).

Eby and colleagues used triple transgenic “Vitesse” mice expressing epidermal melanocytes, melanocyte-reactive T cells, and HLA-A2 to rapidly induce depigmentation in a manner analogous to human vitiligo. These mice had 2.5-fold increased numbers of spontaneous and 6.3-fold increased numbers of inducible IL-17A-producing mononuclear cells compared to the control mice ($p=0.0281$ and $p=0.0091$, respectively). Vitesse splenocytes also exhibited significantly higher IL-17A secretion ($p=0.0281$). The authors noted 3-fold increased antigen-specific IL-17A secretion from Vitesse T cells upon stimulation with cognate

peptide (p=0.0184). Finally, the number of circulating IL-17 secreting T cells as well as IL-17 tissue expression increased 1.3-fold (p=0.0039) and 27.2-fold (p=0.0004), respectively in response to tyrosinase presentation, while the number of IFN-gamma-secreting cells did not[67].

Similar trends have been reported in an IFN-gamma-deficient transgenic mouse model expressing a tyrosinase-reactive T cell receptor (TCR). Upon depletion of Tregs, which normally function to keep auto-reactive T cells in check, the transgenic TCRs had increased IL-17 secretion ($p<0.01$). This trend was also seen after antigen-specific TCR stimulation with cognate peptide ($p<0.01$). Additionally, there were increased numbers of IL-17+ T cells seen infiltrating the skin of these mice ($p<0.01$)[68].

Lastly the inducible costimulator (ICOS), which is important for the functional maintenance of IL-17-secreting T cells, has also been used to study development of autoimmune vitiligo in mice. Infusion of an ICOS agonist has been reported to enhance the capacity to induce autoimmune vitiligo compared to an IgG control (p=0.003), while infusion of an ICOS antagonist impairs the capacity to induce autoimmune vitiligo ($p<0.05$)[69].

5. Putative roles for IL-17 in vitiligo pathogenesis

Th17 cells are critical mediators of defense against extracellular microbes, and as such can coordinate a wide array of physiological responses from a variety of cell types. Numerous facets of their role in this defense, mediated largely by their prototypical effector molecule IL-17, may exacerbate autoimmune inflammation in vitiligo. IL-17 is a potent producer of the chemokine CCL20, a homing molecule that can attract cytotoxic CD8+ T cells from systemic circulation into peripheral tissues[70–72]. CD8+ T cells kill self-cells upon antigen recognition and form a critical component of adaptive immunity. These cells have been implicated in the direct killing of melanocytes in vitiligo models[60,73], and thus their recruitment by IL-17 may play an important role in disease pathogenesis[44,74–76].

IL-17 stimulates endothelial expression of E- and P-selectins as well as the adhesion molecules ICAM-1 and VCAM-1, to enhance neutrophil migration [77]. IL-17 also stimulates keratinocytes to release several chemokines that result in further T cell, neutrophil, macrophage, and dendritic cell influx[78]. The presence of infiltrating macrophages and T cells has been shown to coincide with loss of melanocytes[79]. In addition, neutrophil influx promotes production of several ROS[80]. Oxidative stress induced by these intermediates, in turn, has been associated with vitiligo. ROS accumulation may be directly toxic to critical cell components, resulting in melanocyte destruction and subsequent skin depigmentation[48]. Interestingly NB-UVB, which has demonstrated clinical efficacy in treating vitiligo[64,65], helps relieve oxidative stress and restore oxidant-antioxidant balance, possibly mediated in part through down-regulation of IL-17[81]. As demonstrated in psoriasis, NB-UVB down-regulates both local and systemic IL-17 resulting in decreased inflammation and clinical improvement of psoriatic lesions[82,83]. Studies reviewed in this article have corroborated that NB-UVB leads to significant reductions in IL-17 expression and simultaneous clinical improvement of vitiliginous lesions, as well.

This trend is suggestive of the substantial role that IL-17 may play in vitiligo pathogenesis and may explain the efficacy of NB-UVB treatment.

Studies on melanoma, a cancer of melanocytes, have also shed light on putative roles for the Th17 program in an anti-melanocyte immune response. Melanocyte-specific T cells were able to clear melanoma and induce vitiligo best when cultured in Th17-polarizing conditions, as opposed to conditions that favored Th1 or Th2 differentiation[73]. As noted previously, IL-17 has been shown to antagonize melanogenesis by decreasing expression of MITF and also promote melanocyte death by down-regulating BCL2[62]. Indeed, melanocyte apoptosis is thought to be one mechanism of depigmentation in vitiligo[84].

IL-17 also induces the production of angiogenic factors such as vascular endothelial growth factor (VEGF)[85]. VEGF is critical in generating new blood vessels and increasing permeability of systemic circulation for the passage of immune cells into peripheral tissues[86,87]. These functions are thought to explain the critical role of VEGF in inflammation, and may also be operative in enhancing migration of melanocyte-reactive T cells to cutaneous melanocytes in vitiligo. Importantly, increased dermal angiogenesis has been documented in vitiligo, primarily in the center of lesions[88,89].

6. Conclusion

In summary, review of the literature suggests that IL-17 is significantly correlated with autoimmune vitiligo and may be an integral factor in its progression and severity. Human studies have demonstrated an increased frequency of circulating Th17 cells and higher serum IL-17 in vitiligo patients that positively correlates with disease duration, extent, and activity. Vitiliginous lesions contain significantly higher numbers of IL-17-secreting Th17 and CD8+ cells as compared to unaffected skin in both healthy controls and patients. Several studies have also demonstrated dramatically increased expression of IL-17 mRNA within vitiliginous lesions that also positively correlates with disease duration and extent. NB-UVB therapy, which has been shown to clinically improve vitiligo, reduces Th17 cell abundance as well as serum and tissue IL-17 levels. Finally, exogenous IL-17 directly antagonizes factors related to melanocyte function and survival, possibly contributing to clinical depigmentation. Mouse studies have further demonstrated that depigmentation correlates with greater IL-17A secretion, which modulates vitiligo development.

Further clinical studies are needed to determine the implications of directly targeting the IL-17 pathway in order to treat vitiligo. IL-17 inhibition has been effective for psoriasis, but resulted in a worsening of Crohn’s disease. It is important to note, however, that the primary sites of inflammation differ between the two diseases (skin versus intestines). Therefore, clinical studies examining the therapeutic effect and any adverse events of IL-17 blockade on vitiligo should be pursued based on current molecular data. Moreover, IL-17 or IL-17 pathway molecules could be investigated as a surrogate marker to measure the response to established treatments in vitiligo, such as NB-UVB therapy. Together, the reviewed studies indicate a strong correlation between IL-17 activity and autoimmune vitiligo; however, further studies are needed to investigate a potential causal role.

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Highlights

- IL-17 and the Th17 program have been implicated in the pathogenesis of several autoimmune and inflammatory disorders.
- Several human and mouse studies have shown that IL-17 is significantly correlated with vitiligo and may play a role in its pathogenesis.
- Serum IL-17 may have utility as a surrogate marker to measure response to UVB and other therapies in vitiligo.
- Clinical studies may be warranted to investigate IL-17 blockade as a potential therapeutic target in vitiligo.

Table 1

Human studies examining IL-17 biomarkers in vitiligo

Study	Patient Demographics	Biomarkers examined	Key Results	Implications
Zhou et al, 2015[50]	45 patients with NSV[1]; 45 healthy controls	Th17 cell frequency (blood) IL-17A and Th17 cytokines (serum)	Increased frequency of Th17 cells in NSV group (P= .001); positively correlated with BSA[2] of lesions (P=.014) Increased expression of IL-17 in NSV group (P= .0145)	Role for Th17 cells in Vit[3] pathogenesis
Jandus et al, 2008[51]	5 patients with Vit; 10 patients with PsA[4]; 10 patients with AS[5]; 10 patients with RA[6]; 25 healthy controls	Th17 cell frequency (blood)	No increased frequency of Th17 cells in Vit vs control group	Sample size not sufficiently powered
Bassiouny et al, 2011[52]	30 patients with Vit; 20 healthy controls	IL-17 cytokine (serum) IL-17 mRNA (skin)	Increased expression of IL-17 in serum and skin of Vit group (P< .001 for both); positively correlated with disease duration and BSA of lesions (P < .05)	Role for IL-17 in Vit pathogenesis, extent, and severity
Khan et al, 2012[53]	45 patients with Vit; 45 healthy controls	IL-17 cytokine (serum)	Increased expression of IL-17 in Vit group (P= .001) Ratio of IL-4: IL-17 significantly lower in patients	Vit may involve immune system shift away from Th2 and towards Th17
Basak et al, 2009[54]	40 patients with Vit; 40 healthy controls	IL-17 cytokine (serum)	SS[7] negative correlation between IL-17 and age of onset in Vit group (P= .011); positive correlation with BSA of lesions (P= .038)	Role for IL-17 in Vit pathogenesis and extent
Elela et al, 2013[55]	84 patients with NSV; 80 healthy controls	IL-17 cytokine (serum) IL-17 mRNA (skin)	Increased expression of IL-17 in serum and skin (P< .001 for both); positively correlated with VASI[8] and VIDA[9]	Role for IL-17 in Vit pathogenesis, extent, and severity
Tembhre et al, 2013[56]	60 patients with active Vit; 20 patients with stable Vit; 25 patients with Vit tx with NB-UVB; 70 healthy controls	IL-17 cytokine (serum)	Increased baseline expression of IL-17 in active Vit vs stable Vit vs control group (P= .001) Decreased expression of IL-17 in Vit group after NB-UVB (P< .001)	Part of NB-UVB[10] therapy efficacy may be through reduction of IL-17 expression
Habeb et al, 2013[58]	15 patients with Vit; 15 healthy controls	IL-17 mRNA (leukocytes)	Increased expression of IL-17 in Vit group (P< .01)	Role for IL-17 in Vit pathogenesis
Esmaeili et al, 2011[57]	15 patients with Vit; 15 healthy controls	IL-17 mRNA (leukocytes)	Increased expression of IL-17 in Vit vs control group, not SS (P= 0.05)	Role for IL-17 in Vit pathogenesis
Van den boorn et al, 2009[60]	15 patients with Vit; biopsies given melanocyte antigen-specific stimulation	IL-17-secreting T cell frequency (skin)	Increased frequency of IL-17 producing CD8+ T cells after stimulation	Role for IL-17 in Vit pathogenesis
Wang et al, 2011[61]	20 patients with NSV	IL-17 mRNA (skin) IL-17-secreting T cell frequency (skin)	Increased expression of IL-17 in lesions vs non-lesions (P< .0069) Increased frequency of IL-17 producing T cells in lesions vs non-lesions (P< .05)	Direct tissue evidence implicating active Th17 cells and IL-17 in Vit skin lesions
Kotobuki et al, 2012[62]	23 patients with Vit; melanocytes tx[11] with IL-17A	Th17 cell frequency (skin) MITF[12] mRNA (melanocytes)	Increased frequency of Th17 cells (P< .05)	IL-17 contributes to local depigmentation through several mechanisms

Study	Patient Demographics	Biomarkers examined	Key Results	Implications
		IL-1, IL-6, TNF-a mRNA (melanocytes)	Decreased expression of MITF and the cytokines after tx with IL-17 (P< .05)	
Hegazy et al, 2014[63]	20 patients with NSV tx with NB-UVB; 20 healthy controls	IL-17 mRNA (skin)	Increased baseline expression of IL-17 in NSV group lesional (P=.003) and perilesional (P= .001) skin Decreased expression of IL-17 after NB-UVB in lesional and perilesional skin (P < .05 for both) IL-17 positively correlated with VASI	Part of NB-UVB therapy efficacy may be through reduction of IL-17 expression
Zhan et al, 2014[66]	51 patients with Vit tx with CO2 laser 51 patients with Vit tx with BCG PSN[13]+ CO2 laser	Th17 cell frequency (blood) IL-17 cytokine (serum) IL-17 mRNA (skin)	Decreased frequency of Th17 cells after NB-UVB (P< .05) Decreased expression of IL-17 in serum and skin after NB-UVB (P< .05)	CO2 laser as potential therapy for Vit by reducing IL-17 and Th17

[1] NSV, non-segmental vitiligo;

[2] BSA, body surface area;

[3] Vit, vitiligo;

[4] PsA, psoriatic arthritis;

[5] AS, ankylosing spondylitis;

[6] RA, rheumatoid arthritis;

[7] SS, statistically significant;

[8] VASI, vitiligo area scoring index;

[9] VIDA, vitiligo disease activity score;

[10] NB-UVB, narrow-band ultraviolet B;

[11] Tx, treated;

[12] MITF, microphthalmia-associated transcription factor;

[13] BCG + PSN, Balillus Calmette-Guerin fraction

Table 2

Mouse studies examining IL-17 biomarkers in vitiligo

Study	Mouse Line	Biomarkers Examined	Key Results	Implications
Eby et al, 2014[67]	Triple transgenic mice expressing epidermal melanocytes, melanocyte-reactive T cells, and HLA-A2[1],	IL-17 expression (splenocytes) (spontaneous and after stimulation) IL-17 expression (T cells) (spontaneous and after Ag[2] presentation) IL-17-producing T cell frequency (spontaneous and after Ag presentation)	Increased IL-17 expression from Vit[3] splenocytes spontaneously (P= .0281) and after stimulation (P= .0091) compared to control Increased expression of IL-17 from Vit T cells spontaneously (P= .0184) and after Ag presentation (P= .0004) compared to control Increased frequency of IL-17-producing T cells in Vit spontaneously (P = .0281) and after Ag presentation (P= .039) compared to control	IL-17 levels are increased in mouse models of autoimmune Vit at baseline and after Ag-specific TCR[4] stimulation
Chatterjee et al, 2014[68]	h3TA2 transgenic mice with T cells with HLA-A2-restricted human tyrosinase peptide reactive TCR	IL-17 expression (splenocytes) IL-17+ cell frequency (skin)	Increased expression of IL-17 from TCR-cognate peptide stimulated splenocytes vs control peptide stimulated splenocytes (P< .01) Increased frequency of IL-17+ cells in Treg[5]-depleted mice compared to Treg-preserved mice (*P*< .0001)	Reduced Tregs cause depigmentation mediated in part via upregulation of IL-17
Nelson et al, 2015[69]	ICOS[6]-deficient and ICOSL[7]-deficient mice	Autoimmune Vit development	ICOS agonist promoted Vit development compared to IgG[8] control (p=0.003) ICOS antagonist impaired capacity to induce Vit (p<0.05)	ICOS directly modulates IL-17 expression, which in turn modulates Vit development

[1] HLA-A2, human leukocyte antigen-A2;

[2] Ag, antigen;

[3] Vit; vitiligo;

[4] TCR, T-cell receptor;

[5] Treg, regulatory T cell;

[6] ICOS, inducible costimulator;

[7] ICOSL, inducible costimulator ligand;

[8] IgG, immunoglobulin G